REMARKS

Status of the Claims

Pending claims

Claims 1 to 88 are pending.

Restriction Requirement and Election

In the restriction requirement dated May 14, 2002, the Patent Office alleged that the pending claims of the application were directed to three separate and distinct inventions under 35 U.S.C. §121:

I. Claims 1-7, 11-13, 17-82 and 87, drawn to a method of ligand screening using nucleic acids, classified in class 435, subclass 6.

II. Claims 1-5, 8-80, 83-87, drawn to a method of ligand screening using proteins, classified in class 435, subclass 7.1.

III. Claim 88, drawn to a cell system, classified in class 435, subclass 240.2.

In response to the Restriction Requirement, Applicants elected Group II, claims 1-5, 8-80, 83-87, drawn to a method of ligand screening using proteins.

The Patent Office further alleged that the claims are directed a first set of patentably distinct species as follows:

Species I – *E. coli* ViaA gene, claim 37

Species II – *E. coli* orf1 gene, claim 38

Species III – *E. coli* lepB gene, claim 39

Species IV – *E. coli* ugpB gene, claim 40

Species V – *E. coli* ddiB gene, claim 41

Species VI – *E. coli* secA gene, claim 42

Species VII – *E. coli* fimF gene, claim 43

Species VIII – *E. coli* fimD gene, claim 43

The Patent Office further alleged that the claims are directed a second set of patentably distinct species as follows:

Species 1 – bacterium

Species 2 – gram negative bacterium

Species 3 – *E. coli*

Species 4 – gram positive bacterium

Species 5 – *Staph. aureus*

Species 6 – fungus

Species 7 – yeast

Species 8 – *Archaebacteria*

Species 9 – pathogen (e.g., viruses)

In response, Applicants elected Species I – *E. coli* ViaA gene, claim 37, and Species 1 – bacterium.

When the elected species is held to be allowable, Applicants are entitled to consideration (examination) of additional species; if all species are held to be allowable, a generic claim should be allowed (MPEP §809.02(c); pg 800-50, 8th Edition, August 2001).

Claims amended, canceled and added in the instant amendment

New claims 89 to 93 are added. Thus, after entry of the instant amendment, claims 1 to 5, 8 to 80, 83 to 93 will be pending and under consideration.

Outstanding Rejections

Claims 1 to 5, 8 to 80, 83 to 88 were rejected under 35 USC §103(a) as allegedly obvious. Applicants respectfully traverse all outstanding objections to the specification and rejections of the claims.

Preliminary amendment and SEQ ID listing

A preliminary amendment and SEQ ID listing were submitted June 01, 2001.

Information Disclosure Statements

Applicants note that four Information Disclosure Statements (IDSs) accompanied by Form 1449s have been filed: on March 13, 2001, June 18, 2001, July 2, 2001, and November 7, 2001.

Applicants note that on page one of the office action box 3 was checked to indicate IDSs were attached. However, no initialed Form 1449s accompanied the instant office

action. Applicants request the Patent Office re-forward the Examiner-initialed copies of the Form 1449s submitted with the four IDSs.

Applicants also note that references designated B (Kamb, USPN 5,955, 275), C (Mirabelli, USPN 5,639,595), F (Timberlake, USPN 5,821,076) and U (the Goosen 1994 Current Opinion Biotech. reference) of the instant PTO-892 form were submitted with the first IDS and Form 1449, mailed to the USPTO on March 13, 2001.

Table 1 of the specification

Applicants submit a copy of a declaration submitted under 37 C.F.R. § 1.132 by co-inventor Dr. R. Allyn Forsyth for the instant application's parent application (issued as USPN 6,228,579, incorporated by reference) re-characterizing plasmids set forth in Table 1.

Support for the Claim Amendments

The specification sets forth an extensive description of the invention in the new claims. Support for claims direct to methods of screening for antimicrobial agents comprising providing a microbial proliferation gene and a first and a second sample of a first microorganism, wherein the microbial proliferation gene is identified by introducing an exogenous nucleic acid into the first microorganism and the exogenous nucleic acid has substantial sequence identity to a microbial gene endogenous to the first microorganism and is derived from a second microorganism, can be found, inter alia, on page 18, lines 1 to 5.

Issues under 35 U.S.C. §103(a)

Claims 1-5, 8-22, 24, 26 to 30, 32, 34 to 36, 44 to 50, 54, 55, 57, 58, 61, 63 to 71, 75, 77 to 80 and 83-87 were rejected under 35 USC 103(a) as allegedly unpatentable over Benton et al., U.S. Patent No. (USPN) 6,037,123 (hereinafter "Benton"), in view of Kamb et al., USPN 5, 955,276, filed March 4, 1997, which is a CIP of a priority document USSN 08/800,664, filed February 14, 1997 (hereinafter "Kamb"), and further in view of Timberlake et al., USPN 5,821,076 (hereinafter "Timberlake").

The Patent Office states that Benton does not teach a method for identification of microbial proliferation genes by using random fragments. Kamb is cited to cure this defect in Benton. Applicants respectfully aver neither Kamb nor any of the references cited by the Patent Office cure the defects in Benton.

Applicants respectfully aver that Benton is further defective in that Benton does not teach or suggest a method for identification of microbial proliferation genes by introducing an exogenous nucleic acid into a microorganism, the exogenous nucleic acid having substantial sequence identity to an endogenous microbial gene, wherein the exogenous nucleic acid is a random fragment or a random sequence, and, identifying the endogenous gene as a microbial proliferation gene by comparing the proliferation or viability of the microorganism when the exogenous nucleic acid is expressed in or introduced into the microorganism with the proliferation or viability of the microorganism when the exogenous nucleic acid is not present or not expressed. Benton does not teach or suggest expressing the microbial proliferation gene in an antisense orientation.

In contrast to the instant invention, Benton identifies essential genes using temperature sensitive mutants (ts mutants), as discussed, inter alia, on column 2, lines 9 to 23, of Benton:

> For the *Staphylococcus aureus* essential genes identified in this invention, the essential nature of the genes was determined by the isolation of growth conditional mutants of *Staphylococcus aureus*, in this case temperature sensitive mutants (ts mutants). Each gene was then identified by isolating recombinant bacteria derived from the growth conditional mutant strains, which would grow under non-permissive conditions but which were not revertants. These recombinant bacteria contained DNA inserts derived from the normal (i.e., wild-type) S. aureus chromosome which encoded non-mutant products which replaced the function of the products of the mutated genes. The fact that a clone having such a recombinant insert can complement the mutant gene product under non-permissive conditions implies that the insert contains essentially a complete gene, since it produces functional product.

See also, e.g., column 8, lines 9 to 27 of Benton:

> Also provided is a method of screening for an antibacterial agent by determining whether a test compound is active against one of the genes identified in the first aspect. In a particular embodiment the method is performed by providing a bacterial strain having a mutant form of a gene selected from the group of genes corresponding to SEQ. ID. NOS. 1-105 or a mutant gene homologous to one of those genes. The mutant form of the gene confers a growth conditional phenotype, e.g., a temperature-sensitive phenotype, on the bacterial strain having that mutant form. A comparison bacterial strain having a normal form of the gene is also provided and the two strains of bacteria are separately contacted with a test compound under semi-permissive growth conditions. The growth of the two strains in the presence of the test compound is then compared; a reduction in the growth

of the bacterial strain having the mutant form compared to the growth of the bacterial strain having the normal form of the gene indicates that the test compound is active against the particular gene. [emphasis added]

See also, e.g., column 14, line 52, to column 15, line 10 of Benton:

I. General Approach for Identification of Target Genes

As was briefly described in the Summary above, this invention concerns essential genes in *Staphylococcus aureus*. ... While such bacterial targets are usually (though not always) proteins, the targets can be identified by first identifying the bacterial genes which encode proteins (or RNA transcripts) that are essential for growth of the bacteria.

Identification of these genes which are essential for growth of the bacteria was accomplished by isolating conditional lethal mutant strains. Such mutant strains will grow under permissive conditions, but will not grow, or grow very poorly under non-permissive conditions. For the bacterial genes described herein, temperature sensitive mutants provided the growth conditional phenotype. The particular gene in each strain which was mutated to confer a growth conditional phenotype was then identified by isolating recombinant derivatives of the mutant strains. These recombinant strains each contained a DNA insert which, when expressed, would complement the defective gene and thus would allow growth under non-permissive conditions. ...

Applicants respectfully aver neither Kamb, Timberlake, nor any of the references cited by the Patent Office cure these defects in Benton.

Kamb does not teach or suggest a method for identification of microbial proliferation genes by introducing an exogenous nucleic acid into a microorganism, the exogenous nucleic acid having substantial sequence identity to an endogenous microbial gene, wherein the exogenous nucleic acid is a random fragment or a random sequence, and, identifying the endogenous gene as a microbial proliferation gene by comparing the proliferation or viability of the microorganism when the exogenous nucleic acid is expressed in or introduced into the microorganism with the proliferation or viability of the microorganism when the exogenous nucleic acid is not present or not expressed.

Kamb does not teach or suggest the claimed methods of the invention. Kamb discusses methods for identifying nucleic acid sequences that affect a cellular phenotype. See, inter alia, the Abstract of Kamb:

Methods for identifying nucleic acid sequences that affect a cellular phenotype are disclosed. The method uses a reporter gene whose level of expression correlates with the phenotype in conjunction with a method or device for measuring the level of reporter

expression. An expression library is introduced into the cells, and those cells exhibiting changes in reporter expression level are selected. Expression library inserts from the selected cells are isolated, thereby providing a sub-library enriched for sequences that affect the phenotype reflected by the reporter. Further rounds of sub-library introduction and cell selection may be carried out to provide additional enrichment. Sequences identified using this method may be used to ascertain the identity of additional molecules involved in generating the cellular phenotype.

See also, inter alia, column 8, lines 10 to 28 of Kamb:

The present invention comprises methods to identify components of genetic pathways in cultured cells from plants and animals, or unicellular organisms such as yeast, bacteria, and fungi. Three basic tools are involved: (1) a reporter gene under the control of a specific cis regulatory element that reflects the phenotypic state of a particular cell; (2) a selection device or method that permits rapid quantitative measurement of the expression levels of the reporter molecule on a cell-by-cell basis; and (3) an expression library of proteins, protein fragments, or peptides ("perturbagens") that can be introduced into the chosen cell population. Sequences are isolated from the expression library based on their ability to alter the activity of the cis regulatory sequence, as read out by the reporter expression level. The method thus comprises a set of tools and techniques that together permit the identification of components of genetic pathways using a pseudo-genetic approach. ...

Timberlake does not teach or suggest the claimed methods of the invention. Timberlake discusses methods for identifying an organism carrying a lethal conditional-sensitive mutation in a gene essential for survival, as discussed, inter alia, on column 1, lines 11 to 26, of Timberlake:

The invention features a method for identifying a strain carrying a lethal conditional-sensitive mutation in a gene essential for survival. The method includes (a) growing organisms (e.g., cells) under first permissive conditions; (b) exposing organisms from step (a) to restrictive conditions for a period of time equivalent to at least two growth cycles (e.g., cell cycles); and (c) shifting the organisms from step (b) to second permissive conditions for a period of time equivalent to at least ten growth cycles (e.g., cell cycles). Following this treatment, mutant organisms which both (i) failed to grow when exposed to the restrictive conditions of step (b), and (ii) failed to resume growth when returned to the second permissive conditions of step (c) are selected (step (d)).

However, to expedite prosecution of the instant application Applicants submit a declaration under 37 C.F.R. § 1.131 to "swear behind" Kamb. In particular, Applicants submit copies of declarations under 37 C.F.R. § 1.131 by the co-inventors Dr. Judith W. Zyskind and Dr. R. Allyn Forsyth, co-inventors of the instant patent application filed on November 14, 1997.

The declarations are accompanied by supporting documentary evidence (see appendix). The declarations were first submitted in support of the parent of the instant application. The present application is a divisional of and claims the benefit of priority under 35 USC 120 of USSN 08/971,090, filed November 14, 1997. The instant application was explicitly incorporated herein by reference in its entirety and for all purposes (see, e.g., application transmittal letter).

In the attached Rule 131 declarations co-inventors Drs. Zyskind and Forsyth declared that they conceived of the claimed invention and reduced it to practice in the United States of America prior to February 14, 1997, which is the filing date of USSSN 08/800,664, which is the priority document for Kamb, filed March 4, 1997. Accordingly, the rejection under 35 U.S.C. §103(a) wherein the invention is allegedly unpatentable over Benton in view of Kamb (and in further view of Timberlake) can be properly withdrawn.

Claims 23, 31, 59 and 60 were rejected under 35 USC 103(a) as allegedly unpatentable over Benton in view of Kamb and further in view of Timberlake and further in view of Gossen et al., Current Opinion Biotechnology (1994) 5:516-520 (hereinafter "Gossen").

The Patent Office states that Benton does not teach a method for identification of microbial proliferation genes by using random fragments. However, Applicants respectfully aver that Benton is further defective in that Benton does not teach or suggest a method for identification of microbial proliferation genes by introducing an exogenous nucleic acid into a microorganism, the exogenous nucleic acid having substantial sequence identity to an endogenous microbial gene, wherein the exogenous nucleic acid is a random fragment or a random sequence, and, identifying the endogenous gene as a microbial proliferation gene by comparing the proliferation or viability of the microorganism when the exogenous nucleic acid is expressed in or introduced into the microorganism with the proliferation or viability of the microorganism when the exogenous nucleic acid is not present or not expressed. Benton does not teach or suggest expressing the microbial proliferation gene in an antisense orientation.

Applicants respectfully aver neither Kamb, Timberlake nor Goosen alone or in combination cure the defects in Benton.

As discussed above, to expedite prosecution of the instant application Applicants submit a declaration under 37 C.F.R. § 1.131 to "swear behind" Kamb. In particular, Applicants

submit copies of declarations under 37 C.F.R. § 1.131 by the co-inventors Dr. Judith W. Zyskind and Dr. R. Allyn Forsyth declaring that they conceived of the claimed invention and reduced it to practice in the United States of America prior to February 14, 1997, which is the filing date of U.S. patent application serial no. (USSSN) 08/800,664, which is the priority document for Kamb, U.S. Patent No. 5,955,275, filed March 4, 1997. Accordingly, the rejection under 35 U.S.C. §103(a) wherein the invention is allegedly unpatentable over Benton in view of Kamb (and in further view of Timberlake and Gossen) can be properly withdrawn.

Claims 25, 33 and 62 were rejected under 35 USC 103(a) as allegedly unpatentable over Benton et al. in view of Kamb and further in view of Timberlake and further in view of Mirabelli et al., U.S. Patent 5,639,595 (hereinafter "Mirabelli").

Applicants respectfully aver neither Kamb, Timberlake, Goosen nor Mirabelli alone or in combination cure the defects in Benton, as discussed above.

As discussed above, to expedite prosecution of the instant application Applicants submit a declaration under 37 C.F.R. § 1.131 to "swear behind" Kamb. In particular, Applicants submit copies of declarations under 37 C.F.R. § 1.131 by the co-inventors Dr. Judith W. Zyskind and Dr. R. Allyn Forsyth declaring that they conceived of the claimed invention and reduced it to practice in the United States of America prior to February 14, 1997, which is the filing date of USSSN 08/800,664, which is the priority document for Kamb, filed March 4, 1997. Accordingly, the rejection under 35 U.S.C. §103(a) wherein the invention is allegedly unpatentable over Benton in view of Kamb (and in further view of Timberlake and Mirabelli) can be properly withdrawn.

Claims 72 to 74 were rejected under 35 USC 103(a) as allegedly unpatentable over Benton in view of Kamb and further in view of Timberlake and further in view of Lam et al., USPN 5,510,240 (hereinafter "Lam").

Applicants respectfully aver neither Kamb, Timberlake nor Lam alone or in combination cure the defects in Benton, as discussed above.

As discussed above, to expedite prosecution of the instant application Applicants submit a declaration under 37 C.F.R. § 1.131 to "swear behind" Kamb. In particular, Applicants

submit copies of declarations under 37 C.F.R. § 1.131 by the co-inventors Dr. Judith W. Zyskind and Dr. R. Allyn Forsyth declaring that they conceived of the claimed invention and reduced it to practice in the United States of America prior to February 14, 1997, which is the filing date of USSSN 08/800,664, which is the priority document for Kamb, filed March 4, 1997. Accordingly, the rejection under 35 U.S.C. §103(a) wherein the invention is allegedly unpatentable over Benton in view of Kamb (and in further view of Timberlake and Lam) can be properly withdrawn.

Claim 76 was rejected under 35 USC 103(a) as allegedly unpatentable over Benton in view of Kamb and further in view of Timberlake and further in view of Matsunaga, et al., USPN 4,788,038 (hereinafter "Matsunaga").

Applicants respectfully aver neither Kamb, Timberlake nor Matsunaga alone or in combination cure the defects in Benton, as discussed above.

As discussed above, to expedite prosecution of the instant application Applicants submit a declaration under 37 C.F.R. § 1.131 to "swear behind" Kamb. In particular, Applicants submit copies of declarations under 37 C.F.R. § 1.131 by the co-inventors Dr. Judith W. Zyskind and Dr. R. Allyn Forsyth declaring that they conceived of the claimed invention and reduced it to practice in the United States of America prior to February 14, 1997, which is the filing date of USSSN 08/800,664, which is the priority document for Kamb 5,955,275, filed March 4, 1997. Accordingly, the rejection under 35 U.S.C. §103(a) wherein the invention is allegedly unpatentable over Benton in view of Kamb (and in further view of Timberlake and Matsunaga) can be properly withdrawn.

Applicants submit the Rule 131 "swearing back" declarations merely to expedite prosecution of the instant application, making no express or implied admissions regarding patentability of the claimed invention in light of the above-cited art and, as noted above, respectfully traverse all outstanding objections to the specification and rejections of the claims.

In view of the above remarks, Applicants respectfully submit that the pending claimed invention is not obvious over the cited art. Accordingly, the rejection under 35 U.S.C. §103(a) can be properly withdrawn.

CONCLUSION

In view of the foregoing amendment and remarks, it is believed that the Examiner can properly withdraw the rejection of the pending claims under 35 U.S.C. §103(a). Applicants believe all claims pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If necessary, please apply additional and necessary charges, and apply all credits, to Deposit Account No. 06-1050.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (858) 678-5070.

Respectfully submitted,

Date: Dec. 27, 2002

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Version with markings to show changes made

In the specification:

The pending title has been replaced with the following new title:

--METHODS FOR IDENTIFYING ANTI-MICROBIAL AGENTS--

On page 1, after the title, the following paragraph has been inserted:

-- CROSS-REFERENCES TO RELATED APPLICATIONS

The present application is a divisional of and claims the benefit of priority under 35 USC 120 of U.S. application serial no. (USSN) 08/971,090, filed November 14, 1997, issued as USPN 6,228,579, on May 8, 2001. This application and patent are explicitly incorporated herein by reference in their entirety and for all purposes.--

In the claims:

New claims 89 to 93 have been added.